Author response

We thank the reviewers for their very thoughtful and constructive comments. Overall, we have attempted, whenever possible, to integrate their suggestions. Please find our specific responses below.

Comments to the Author(s):

Reviewer # 00188507

The authors carefully studied their liver tissues and described the clinical characteristics of the rare condition of non-obstructive SD. The information are well summarized and can be helpful for the hepatologist, therefore, it is acceptable after the careful check/corrections of the grammatical errors, typos, formatting, and language editing.

Author response: We appreciate the comment. We have performed a careful check for grammatical errors and typos with additional edits.

Reviewer # 00070845

Excellent paper. Beyond the roles of IL-6 and VEGY, I would be interested to know any further thoughts as to the mechanism(s) of dilatation in these patients without obstruction.

Author response: Unfortunately, little is known about the mechanisms involved in nonobstructive SD, partly due to the rare nature of this condition. Further studies, particularly in experimental models may be helpful to elucidate the pathophysiology of SD.

Reviewer # 03475479

In present study, authors showed the prevalence of SD and discussed the clinical impact. It is interesting, but several issues listed below should be addressed.

Abstract In conclusion sentence, HPA was not mentioned and discussed in the manuscript.

Author response: Thank you for your comment. We identified 51 patients (58%) with findings consistent with HPA. We did not identify a correlation between the presence of HPA and the different etiologies.

Method: Ethical consideration should be mentioned.

Author response: This has been added to the title page as listed on the guidelines and requirements for manuscript revision.

Authors should describe whether hepatic vascular abnormalities were checked by imaging studies in all cases included in this study.

Author response: Thank you for your comment. Abdominal ultrasound with Doppler was performed in all patients to rule out venous outflow obstruction. Abdominal CT with contrast and abdominal MRI images were available for review in nine and five patients respectively. We did not identify hepatic vascular abnormalities, such as HHT or Abernethy malformation.

Authors should define 'Inflammatory conditions' or 'Autoimmune disorder'.

Author response: Thank you for the comment. The definitions have been added to the methods section.

In Table 3, it was unclear what is compared.

Author response: We apologize for the confusion. Table 3 reports the frequency of hepatic nodules, ascites, portal hypertension, and splenomegaly stratified according to possible etiologies.

Authors should mention how 'medication related' was defined.

Author response: This has been added to the methods section.

Authors discussed the possible role of IL-6 and VEGF in the development of SD. Immunohistochemical staining by IL-6, L-6R or VEGF in present liver samples might support the idea.

Author response: We agree with the reviewer. This is an excellent idea which we may consider in future studies.

As authors showed, the etiology of SD was diverse. Therefore the clinical significance of SD was unclear. As authors discussed, the clinical outcome in SD cases with unspecified cause might be important to clarify the clinical impact of SD.

Author response: Thank you for the excellent suggestion. We have separated the outcomes for the undefined group in the results and discussion sections.

Oxaliplatin is known as a contributor of hepatic SOS by inducing endothelial damages.

Author response: We agree with the reviewer. Although none of our patients met all histologic criteria for SOS it is possible that some of these patients either had early SOS or NRH, both of which have been reported in association with oxaliplatin. This is further supported by the high prevalence of noncirrhotic portal hypertension in this subset of patients.

Authors should show more detail about other histological findings in present cohort and discuss the relation with SD.

Author response: We appreciate the comment. We have listed all histologic findings on table 6 and we have included a column reporting the overall rate of each separate histologic feature in association with SD.

Reviewer # 00051373

An interesting topic talking about the isolated hepatic non-obstruction sinusoidal dilatation but not well writing and missing interpretation. Frist of all, this is a single arm without control group observation study. It looks like a big data around 491 cases analysis but finally only 88 cases to be investigated in 20 years. The causes of non-obstruction sinusoidal dilatation are not clear after go through the whole manuscript. Particularly, the inflammatory disorder is around 32 % but only 1 to 2 cases in each other inflammatory diseases.

In contrast, most of the hematologic disorder seems to be a major finding here. The causes of death regarding to the non-obstruction sinusoidal dilatation need to be more detail describe.

Author response: thank you for your comment. This has been added to the result section.

The positive findings on AST/ALT, serum total bilirubin and ascites need to be interpretation more detail regarding to the non-obstruction sinusoidal dilatation.

Author response: thank you for your comment. Elevated transaminases in the setting of hyperbilirubinemia and ascites possibly represent drug-related sinusoidal obstruction syndrome. We have added this to our result and discussion section.

On the mortality investigation, C-M survival cure is a very important in this study.

Author response: thank you for your comment. Kaplan-Meier survival curve analysis was done with no significant difference among the groups. Additionally, survival in our study is not directly attributed to SD, but rather related to the underlying associated etiology. So not to confuse the readers, this was not included in the results.

All figures are not being viable for reviewing. Finally, there is no meaning in table 5 and 6.

Author response: thank you for your comment. We have re-uploaded the figures. Table 5 and 6 refers to pattern of liver injury and histological findings (pattern of sinusoidal dilatation, fibrosis pattern, HPA, RBC extravasation, etc) stratified by different etiologies. Unfortunately, we did not identify an association between pattern of liver injury or histological findings and different etiologies of sinusoidal dilatation.